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Albendazole and mebendazole have low efficacy against *Trichuris trichiura* in school-age children in Kabale District, Uganda

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Introduction

Albendazole and mebendazole, used as one dose treatments, are the drugs of choice in current control programmes of the soil-transmitted helminths, *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm. The efficacy of both drugs is high against *A. lumbricoides*, moderate against hookworms, but unsatisfactory against *T. trichiura*. A recent systematic review and meta-analysis reported cure rates for *T. trichiura* infection following treatment of 28% (one dose 400 mg albendazole) and 36% (one dose 500 mg mebendazole).
In Jamaica, adult *T. trichiura* worms were successful recovered from human faeces using one dose 400 mg albendazole, one dose 400 mg albendazole given daily for 2 days or 100 mg mebendazole given twice daily for 3 days. High numbers of worms were recovered on the last day of treatment and the following two days (on days 3 to 5), while none were recovered on day 6.
The present study investigated cure and egg reduction rates of one dose 400 mg albendazole in school-age children infected with *T. trichiura*, and recovered adult worms after treatment with twice daily doses of 100 mg mebendazole for 3 or 5 days, respectively.

Materials and methods

The studies were implemented in Kabale District in the South-western part of Uganda in school-age children in March 2005, in June 2007 and in January 2008. Children were screened for *T. trichiura* using Kato-Katz cellophane thick smear of 41.7 mg of stool.

Albendazole study
Infected children were selected and the determination of egg counts of *T. trichiura* infections was carried out at baseline and at days 7 and 14 post-treatment. After baseline examination all children were treated with a single dose of albendazole (400 mg tablet, GlaxoSmithKline Beecham).

Mebendazole studies
T. trichiura infected children with at least 120 eggs per gram (epg) of faeces were included in each of these studies. The children were treated with 100 mg mebendazole (tablet, Johnson and Johnson) twice a day for 3 days or 5 days, respectively.
24 hours faecal samples were collected starting on the last day of treatment and continued for 3 days or 7 days, respectively. The collected stool was sieved (mesh size app. 250µm) and all *T. trichiura* worms were counted.

Results

Albendazole study

A total of 70 *T. trichiura* infected children with the mean (min-max) age of 11.2 (6-15) years were included in the study. Of these 49% (34/70) were girls and 51% (36/70) boys. Seven and 14 days post-treatment, 66 and 67 children, respectively, delivered stool for examination (Table 1). Seven days post-treatment only 5 children were negative for *T. trichiura* eggs giving a cure of 8% (5/66) and an geometric mean egg reduction of 89% (536/605, $P<0.001$). At day 14 post-treatment, all children were positive and the egg counts had increased from day 7 ($P<0.001$) and was 57% (342/605) of the baseline level ($P<0.001$).

Table 1. Number of school children infected with *Trichuris trichiura* (egg positive) and the arithmetic and geometric mean intensity (geo mean epg) before and 7 and 14 days post-treatment with one oral dose of 400 mg albendazole.

	Pre-treatment	7 days post-treatment	14 days post-treatment
Number of children examined	70	66	67
Number infected	70	61	67
Arithmetic mean epg (95% CI)[a]	927 (713 - 1142)	181 (117 - 245)	529 (397 - 660)
Geo mean epg (95% CI)[a]	605 (480 - 763)[b]	69 (45 - 105)[b]	342 (268 - 436)[b]

[a] 95% confidence intervals (95% CI)
[b] Geometric mean intensities were all significantly different from each other ($P<0.001$, paired t-test)

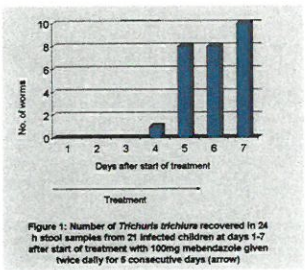

Figure 1: Number of *Trichuris trichiura* recovered in 24 h stool samples from 21 infected children at days 1-7 after start of treatment with 100mg mebendazole given twice daily for 5 consecutive days (arrow)

Mebendazole studies

In the 3 days treatment study, 34 *T. trichiura* infected schoolchildren with a mean age (min-max) of 11.0 (7-15 years) and arithmetic and geometric mean intensities of 906 (558-1255) and 673 (528-859) epg were included. During the 3 days of faeces collection, 4 adult worms were recovered from 2 children. These 2 children initially had 624 and 1200 epg.

In the 5 days treatment study, 35 *T. trichiura* infected school-aged children were included. Of these, 21 delivered 24 h stool samples for all 7 days. The baseline arithmetic and geometric mean intensities (95% CI) of these 21 children were 542 (369-715) and 423 (301-594) epg, respectively. Ten of these children expelled a total of 27 adult *T. trichiura* worms (4 children provided 1; 2 provided 2; 2 provided 3; 1 provided 5 and 1provided 8 worms). The 10 children had the following baseline egg counts: 1 worm expelled: 144, 360, 456 and 480 epg; 2 worms expelled: 240 and 816 epg; 3 worms expelled: 648 and 1440 epg; 5 worms expelled: 648 epg; 8 worms expelled: 1248 epg. The first worm appeared on day 4 post-treatment (Figure 1).

Discussion

In the albendazole study egg counts decreased at day 7, but increased again at day 14, suggesting that worms were not killed but their metabolism temporarily reduced.

Taking a mean of daily stool production of 200 g per child and an egg count of 500 epg, the daily egg excretion will be 100 000 eggs per day. As a female *T. trichiura* may shed between 3000 and 20 000 eggs per day, each child is expected to harbour between 5 and 30 gravid female worms or approximately 10-60 adult *T. trichiura* worms, assuming a 1:1 sex ratio. The 5 days mebendazole treatment study retrieved less than one worm per child during a 4 days period despite a arithmetic mean egg count before treatment of 542 epg. Our low numbers may be due to too early termination of stool collection as the highest number of worms were recovered on day 7, when the study ended. In any case we found a delayed expulsion pattern compared to other studies, which obtained maximum numbers on days 3-5, and none at day 6.

In conclusion, we found that even with the longest treatment regimen applied (twice daily for 5 days) and collection of stool samples over 7 consecutive days only very few adult worms were recovered. Furthermore, the low cure and egg reduction rate of albendazole and the fact that the egg reduction is only temporary, suggest that alternative drugs and/or alternative regimens in current control programmes against *T. trichiura* need renewed attention.